

Chemical reaction scheme for the synthesis of a peptide-oligonucleotide conjugate:

Starting Materials:

- Peptide:** $\text{H}_2\text{N}-\text{N}(\text{Tn})-\text{PEPTIDE}-\text{C}(\text{Boc})-\text{CO}-\text{S}_1$
- Oligonucleotide:** $\text{HO}-5' \text{ OLIGONUCLEOTIDE } 3'-\text{S}_2$

Reaction 1 (Peptide): 1. $\text{Bns}-\text{CH}_2-\text{CH}_2-\text{C}(=\text{O})-\text{OPfp}$

Reaction 2 (Peptide): 2. 90% TFA

Reaction 1 (Oligonucleotide): 1. $\text{tBuSS}-\text{CH}(\text{NHf-moc})-\text{CONH}-\text{O-P}(\text{NPr}_2)(\text{OCE})$

Reaction 2 (Oligonucleotide): 2. eq. NH_4OH

Intermediate Peptide: $\text{CONH}-\text{N}(\text{PEPTIDE})-\text{C}-\text{CONH}_2$ (with $\text{O}-\text{SBn}$ group)

Intermediate Oligonucleotide: $\text{tBuSS}-\text{CH}(\text{NH}_2)-\text{CONH}-5' \text{ OLIGONUCLEOTIDE } 3'-\text{OH}$ (with O^- groups)

Coupling: TCEP/PbSH/DMF/aq. buffer, pH 7.5

Final Conjugate: $\text{CONH}-\text{N}(\text{PEPTIDE})-\text{C}-\text{CONH}_2$ linked to $\text{SH}-\text{CH}(\text{NHf-moc})-\text{CONH}-5' \text{ OLIGONUCLEOTIDE } 3'-\text{OH}$ (with O^- groups)

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FIGURE 2

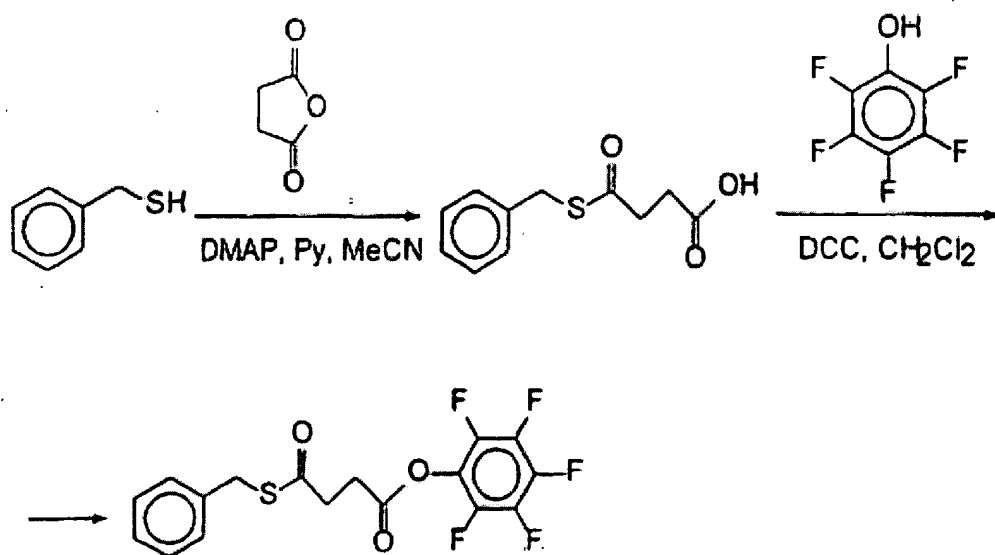
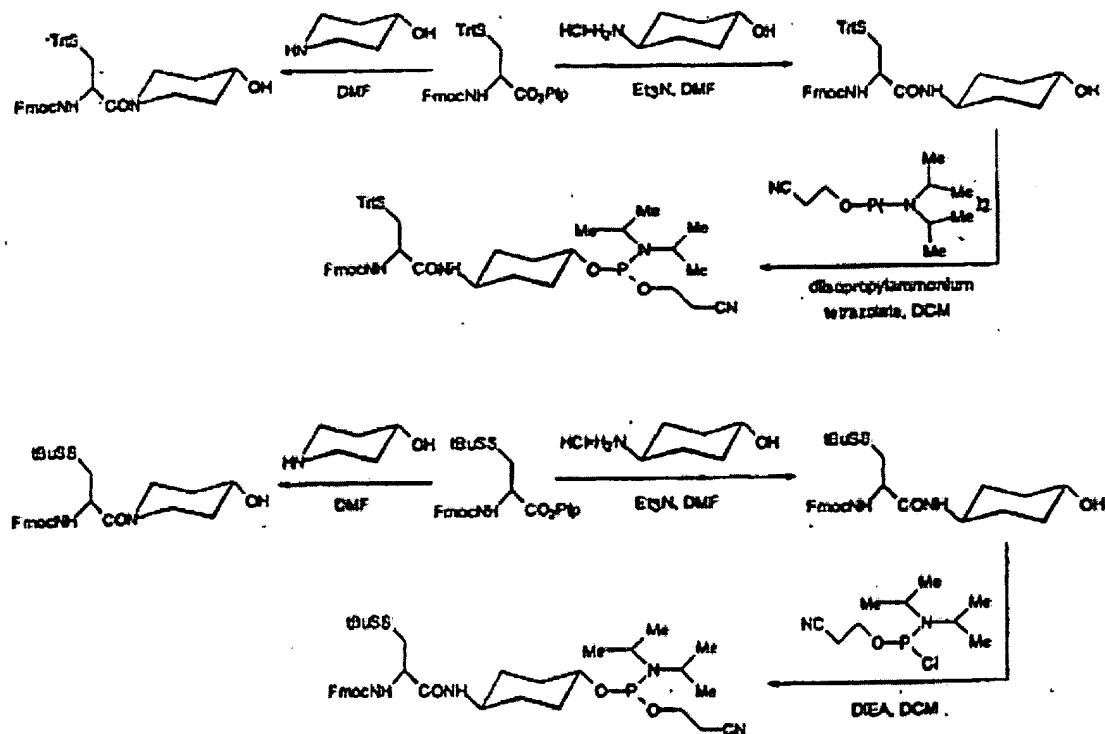


FIGURE 3



Reaction Scheme 3: Syntheses of coupling reagent (IV)